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| EXAMINER | |
|---|---|
| TRAN, SUSAN T | |

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| 1615 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/784,900 | COOPER ET AL. | |
| | Examiner | Art Unit | |
| | S. TRAN | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,6-8,16,18-52,55-57,64-72,87,88 and 90-100* is/are pending in the application.

4a) Of the above claim(s) *26-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,16,18-25,50-52,55-57,64-72,87,88 and 90-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/27/10;10/19/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/814240 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Claim Rejections - 35 USC § 103***

*Claims 1-3, 6-8, 16, 50-52, 55-57, 64-67, 87, 88 and 90-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. WO 99/09988 A1, in view of Liversidge et al. WO 9325190 a1.*

Struengmann teaches a pharmaceutical composition comprising micronized meloxicam with suitable additive such as microcrystalline cellulose and/or surfactant and/or co-solvent (page 3; and examples). Surfactant is disclosed at page 4, last paragraph bridging page 5. Co-solvent includes propylene glycol, polyethylene glycol, glycerol and ethanol (page 3, last paragraph). The obtained meloxicam is then incorporated into dosage forms include controlled release oral composition, tablet, sachet, ointment, suppositories, and hydrogel (page 5, paragraphs 35).

Struengmann does not expressly teach the particle diameter of the micronized meloxicam. However, one of ordinary skill in the art would have been motivated to, by routine experiment optimize the particle size with the expectation of at least similar results. This is because it is known in the art to reduce particle size of a drug to obtain a higher bioavailability of said drug. Liversidge teaches a process of preparing nanoparticulate drug substances comprising the steps of dispersing a crystalline drug in a liquid dispersion medium containing a surface modifier, and subjecting the premix to mechanical means to reduce the particles size of the drug substance to less than 400

nm (pages 7-10). Drug includes water-insoluble drug substance such as analgesic and NSAID substances including oxicam (page 3). Surface modifier includes nonionic, anionic, organic, inorganic excipients, and mixture of two or more (pages 5-6). Surface modifier includes polyvinyl pyrrolidone (page 6). Liversidge further teaches the surface modifier is adsorbed on the surface of the drug substance, but the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages (page 6, lines 25-31). Liversidge also teaches the nanoparticles are combined with pharmaceutically acceptable carrier suitable for parenteral injection (page 11, lines 29-35).

Thus, it would have been obvious to one of ordinary skill in the art to modify the meloxicam composition of Struengmann to obtain a nanoparticulate meloxicam composition in view of the teachings of Liversidge. This is because Liversidge teaches a nanoparticulate composition that exhibits unexpectedly rapid onset (bioavailability) (page 12, lines 11-14), because Liversidge teaches a process suitable for a wide variety of NSAIDs including oxicam, because Struengmann teaches the desirability for obtaining a composition with high bioavailability, and because Struengmann teaches reducing particle size of meloxicam by micronisation (page 3, last paragraph; page 10; and examples).

It is noted that Struengmann does not explicitly teach the claimed properties such as the $C_{max}$ values. However, it would have been obvious to one of ordinary skill in the art to, by routine experimentation obtain the $C_{max}$ value that falls within the claimed range, because Liversidge teaches nanoparticulate having the claimed particle size in a

dispersion for parenteral injection exhibits the claimed $C_{max}$ value, e.g., 187 µg/mL (page 16).

*Claims 18-25, 68-72 and 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struengmann et al. in view of Liversidge et al., and Desai et al. WO 01/45706 A1 or Courteille et al. US 5,384,124.*

Struengmann is relied upon for the reasons stated above. Struengmann does not teach the second particle population.

Desai teaches a dual-release composition of low water soluble drug (COX-2 inhibitor) comprising first fraction of the drug in nano-particulate form having average diameter of about 200 to about 400 nm and a D90 particle size less then about 5 µm (page 18); and a second fraction of the drug in micro-particulate form having $D_{10}$ particle size of between 25 to about 100 µm (page 20, 1st paragraph). The first fraction nano-particle drug can be present alone or in combination with one or more excipient, such as nano-particles of the drug have a surface modifying agent (PEG-400) adsorbed on the surface thereof (page 18, 3rd through page 19). The weight ratio of the first to the second fraction of the drug in the composition is about 1:10 to about 10:1 (page 22, 3rd paragraph). The composition can be in an oral dosage form including tablet, pills, hard or soft capsule, lozenges, cachets, dispensable powder, granule, suspension or elixir (pages 37-38).

Courteille teaches a solid unitary composition comprising combination of nano-particle having diameter of less than 1 µm and micro-particle having diameter of

between 1 µm to 2 mm (see abstract, column 2, lines 32-46). The mixture of nano/micro-particle contains one or more active agents of the same or different type (column 1, lines 66-68, and column 2, lines 23-31). The active agent can be selected from antibiotic, analgesic, tranquilizer, vitamins, and therapeutic agents for diseases of allergies, hormones, or gastrointestinal tract (column 5, lines 46-66). The mixture of nano/micro-particle is prepared by any known method (air-fluidized bed coating, turbine coating, simple extrusion, or micro-encapsulation) employing the use of a polymer or a macromolecular substance (surface stabilizer) selected from the group of cellulose derivatives, starch, polyamide, collagen, dextrin, gelatin, polyvinyl chloride or the like (column 2, lines 46-55, and column 3, lines 18-40). The mixture further comprises stabilizing agent, surfactant, and biding agent (column 4, lines 20 through column 5, lines 1-28). Courteille further teaches the solid dosage form comprises immediate release with a secondary controlled release of mixture of nano/micro-particle (column 6, lines 16-50). The solid dosage form is to be incorporated into pharmaceutical oral dosage form (column 6, lines 51-56).

Thus, it would have been obvious to one of ordinary skill in the art to modify the composition of Struengmann to include the second particle population in view of the teachings of Desai or Courteille, because Desai and Courteille teach compositions suitable for analgesic substance, because Desai and Courteille teach that combination of one or more population of active substance with different particle size is well known in the art, and because Struengmann teaches the desirability for formulating a controlled

release composition comprising different layer having different release profiles (page 5, 3-4 paragraphs).

***Response to Arguments***

Applicant's arguments filed 08/17/10 have been fully considered but they are not persuasive. Applicant's arguments have been addressed in the advisory action dated 09/01/10. The arguments are reiterated herein.

Applicant argues that Struengmann fails to fairly teach or suggest numerous other claim limitations, including the specific particle size. Struengmann fails to teach the specific surface stabilizers, their structural relationship to the particles, and that they are free of intermolecular cross-linkages. Thus, to combine the references as proposed in the rejection (to simply render the particles of Struengmann in the size of Liversidge) is not a straight-forward exercise as set forth by the rejection. For even if a person of ordinary skill in the art were to do this, (reduce the particles of meloxicam in Struengmann to the claimed range), Struengmann still fails to teach the specific surface stabilizers, their structural relationship to the particles, and that they are free of intennolecular cross-linkages.

Applicant further argues that Liversidge may fairly teach or suggest reduction in particle size to obtain higher bioavailability, but there is no reason for one skilled in the art to do this to the meloxicam of Struengmann because Struengmann already employs techniques to improve solubility and bioavailability. Struengmann discloses a solution for improving solubility and bioavailability "by mixing meloxicam with special additives"

rather than by reducing the particle size to the nanoparticulate range. The special additives include surfactants, co-solvents, hydrotropic agents, alkalizing agents, cyclodextrins, hydrocolloids and polymers. *See* page 3, lines 4-16. There is no suggestion by Struengrnann that its methods fbr improving dissolution and bioavailability are in anyway insufficient and 1 ) would benefit by further reduction in particles size in view of Liversidge, and/or 2) would be possible using the techniques described in Liversidge.

However, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Struengmann teaches co-micronized the active agent and the surfactant. Hence, the burden is shifted to applicant to show that the surfactant taught in Struengmann does not associate with the surface of the active nanoparticles. Further, Struengmann is cited in combination with the Liversidge patent, which teaches the association of surface modifier on the surface of the active drug, and the adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages (page 6, lines 25-31). It is noted that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d

347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Applicant argues that the Examiner points out that "Liversidge teaches a process suitable for a wide variety of NSAIDs including oxicam" (final Office Action, page 7, lines 11-12). In order to advance prosecution, Applicants preemptively rebut a rejection in which Liversidge is used as the primary reference where one might state that it would be obvious to select the meloxicam of Struengmann in the process of Liversidge. Liversidge fails to expressly state meloxicam as an exemplary NSAID. Liversidge does disclose many exemplary NSAIDs at page 4, line 16, through page 5, line 4, and oxicam is one of the exemplified subgenus. Pursuant to MPEP 2144.08, the prior-art teaching of a genus does not necessarily renders the claimed species obvious. *See* the discussion submitted in the response filed on June 29, 2009, pages 31-32. Moreover, Liversidge discloses numerous surface modifiers at page 5, line 10, through page 6, line 24. In the absence of any teaching or fair suggestion from the cited reference, one skilled in the art would not have considered it obvious to select polyvinylpyrrolidone and sodium deoxycholate as the surface stabilizers, to obtain the claimed invention prescribed by claims 1 and 50.

However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would

have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Liversidge teaches a method for preparing a delivery system useful for a wide variety of active agents that include an NSAID. Struengmann teaches the desirability for preparing a delivery device that is useful for the delivery of an NSAID.

Accordingly, for at least the above reasons, the 103(a) rejections of record are maintained.

## ***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1615